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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,521	HERWEIJER ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This application claims benefit to provisional application 60/225,946 filed August 17, 2000.

Applicants' amendment filed August 11, 2003 has bee received and entered. Claims 1, 8, 10, 12 and 18 have been amended. Claims 1-20 are pending and currently under examination.

Information Disclosure Statement

The Zhou *et al.* (J. Mol. Biol., 1997) filed August 12, 2003, has been received. The reference fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. The reference has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

The objection to claims 1 and 18 because the claims include internal periods in the listing of each of the steps is withdrawn. The amendments to the claims have obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

In the instant case, the limitation that expressing the 'transgene for longer that 7 days at levels 20% higher than the nucleic acid sequence present in a circular or supercoiled nucleic acid' is considered new matter. Initially, it is noted that the portions of the specification pointed to and relied upon by Applicants are the working examples. First, upon review of the specification Examiner can not find literal nor figurative support for the embodiment of 20%. Even calculating the various percentages represented at different times in Example 5, the percentages range from 14% to 385/<1 (page 23), not 20%. More importantly, the numbers and times recited in the claims are not specifically associated even in passing with the generic concept Applicants consider the inventive concept of the invention. At most, the limitations would only support a specific method including all the particulars of the example from which they are taken. The situation is analogous to that decided by the courts in *Purdue Pharma L.P. v.*

Faulding Inc. (56 USPQ 2D 1481 99-1416-1433, CAFC 2000) where specific characteristics from examples were found not to be supported in the general disclosure of the genus claimed. In the instant case, there is nothing in the specification that teaches even in passing that expression at levels 20% higher or expression for longer that 7 days was specifically contemplated, or that it pertains specifically to the generic aspect of providing a linear nucleic acid, or even if it is enabled for the full breadth of all the various types of nucleic acids encompassed by the claims (see specification at page 7, lines 14-23). Upon review of the entire specification, there is no specific teaching which provides particular guidance of practicing step (a) to result specifically in step (b) as presently amended, nor is the specific teaching that the specific expression recited in step (b) was contemplated to apply generally to practicing step (a) or all the possible nucleic acid sequences embraced for use in step (a). In summary, the specification fails to provide any description of the polynucleotides to be delivered that would result in the expression required by the instant claims. The dependent claims are included in the basis of the rejection because they fail to describe any particular element of the nucleic acid being delivered that would result in the expression levels recited, and as discussed above it does not appear that from the working examples nor from the specification in general that the particular expression levels required in practicing the method were specifically contemplated for any of limitations set forth in the dependent claims.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-20 are also rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. As discussed above, the specification fails to provide any guidance on any particular elements comprised by the nucleic acid sequences being delivered, that would result in the activity required in practicing the claimed method. The claims are very broad encompassing the use of any polynucleotide that results in particular expression levels once delivered, however the single working example comparing expression of a single cut and uncut plasmid pMIR7 fails to adequately describe all the nucleic acids encompassed by the claims, and thus fails to adequately describe the starting materials even if the artisan were to try to test any possible nucleic acid sequence to see if it is encompassed by the claim. Further, even though nucleic acid sequences could theoretically be tested for expression levels, the specification provides no specific guidance on how this would be performed at any level of expression, *i.e.* protein or RNA levels, how similar or dissimilar the nucleic acid sequence can be when comparing a linear sequence to that of a sequence comprised in a circular or supercoiled plasmid form, nor does the specification provide any guidance on when such measurements should be taken in order to determine if the polynucleotide meets the limitation required by the claims. Finally, it is unclear that the expression seen in the single working example examining one cut and uncut plasmid sequence would universally apply to all types or lengths of sequences comprised by the claims. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the

art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Initially, it is noted the amendments to the claims has obviated the basis of each of the specific rejections of record set forth in the previous office action.

Newly amended claims 1 and 18 are vague and unclear in the recitation of "at levels 20% higher than the nucleic acid sequence present in a circular or supercoiled nucleic acid" because how and when such a measurement is made is not clearly set forth. The metes and bounds of the claim are unclear because what is being measured, *i.e.* RNA, protein, and the types or characteristics of nucleic acid sequences being delivered are not clearly set forth, nor is the time when the measurement is made. Neither the claim nor the specification provides a clear nexus between step (a) delivering and step (b) expressing that results in the functional limitation added to the claim. It appears that simply providing the nucleic acid would or should inherently result in step (b), however the specification does not specifically support this analysis. Further, changes affected by the time at which this embodiment of expression is measured make the claim indefinite. For example, once the nucleic acid is delivered, one would not expect any significant amount of expression from either linear or circular sequences, however at a later time a difference may (or may not) be observed, and subsequently at an even later time expression in neither case will be detectable. Thus, practicing step (a) would result in a method that initially and finally result in a non-infringing method, however at some undetermined time between these points there may be conditions which may meet the limitations (as generally supported by working example 5 analyzing pMIR7 expression). The claim is indefinite because the only means to know if one were infringing the claim would be to provide a relative comparison when

the method is being practiced for each polynucleotide comprised by the claims. Dependent claims are included in the basis of the rejection because they only set forth structural features of the nucleic acid used in the method without indicating how they influence expression levels or how they may or may not affect the time of expression.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7, 18 and 19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wolff *et al.* (Science, 1990).

Claims 1, 2, 5, 7-13, 18 and 19 stand rejected under 35 U.S.C. 102(a) as being anticipated by Goryshin *et al.* (Nature Biotech, 2000) as evidenced by Gibco BRL (page 14-19).

Claims 1, 2, 5, 7-13, 18 and 19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tucker *et al.* (US Patent 5,102,797, issued 1992) as evidenced by Gibco BRL (page 14-19).

Claims 1, 16, 17 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rolland *et al.* (US Patent 6,514,947).

Applicants note the amendments to the claims and argue that none of the cited references teach that delivery of the single stranded polynucleotide resulted in expression of a 'transgene for longer that 7 days at levels 20% higher than the nucleic acid sequence present in a circular or supercoiled nucleic acid'. Applicants acknowledge that each reference teaches delivery of a single stranded polynucleotide. Further, it is noted that Applicants do not argue that embodiments in dependent claims are not provided, only that none of the references provide specific support for the expression levels recited and required by the amended claims. See Applicants' amendment, bottom of page 4. Applicants' arguments have been fully considered, but not found persuasive.

As acknowledged by Applicants' and set forth in the basis of the rejection, each of the cited references provide specific teachings to anticipate the structural limitations of practicing the method as claimed. Further, Examiner would agree that none of the references specifically compare the expression levels of a linear versus a circular polynucleotide sequence, and do not specifically teach the functional limitation recited in the amended claims. However, where, as here, the claimed and prior art process are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess

the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, or "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw,* 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, because the teachings of Wolff *et al.*, Goryshin *et al.*, Tucker *et al.* and Rolland *et al.* meet the structural limitations for practicing the methods as claimed, one would consider any functional limitation resulting from this practice would inherently result in the functional limitation set forth in step (b). Further, given the general and limited guidance of the specification for the types of polynucleotides contemplated for use in the claimed methods, there is no teaching nor evidence that any particular sequence that is provided in a linear form would not inherently result in the specific expression levels recited and required by the instant claims. Therefore, even though Wolff *et al.*, Goryshin *et al.*, Tucker *et al.* and Rolland *et al.* do not specifically teach the functional limitation set forth in the claims that Applicants argue distinguishes the claimed invention from that disclosed, simply delivering any linear polynucleotide sequence would inherently result in this functional limitation.

As set forth in the previous office action, Wolff *et al.* teach the direct transfer RNA and expression of the encoded gene into mouse muscle. In particular, Wolff *et al.* teach that RNA can be generated from a plasmid (page 1468, ref 26)(claim 7) and that when injected provided expression of a marker gene for several hours (solid bar in graph in figure 3). The limitations of

blunt ends, sticky ends and chimeric ends are not specifically defined in the specification, however as they would apply to a single stranded RNA molecule, a ssRNA has blunted end which because it is single stranded could anneal to other polynucleotides and thus be interpreted as blunt ended and sticky ended nucleic acids. Further, the two ends of the RNA generated, the 5' and 3' ends, are two different sequences so they could be considered chimeric ends. Wolff *et al.* describe the construction of the plasmid used to make the linear RNA, and teach that restriction enzyme digests were used to sub-clone the various fragments (page 1468, ref 12)(claims 18 and 19).

Goryshin *et al.* describe an *in vivo* method using a transposition system to insert exogenous nucleic acid sequences (see summary in abstract). More specifically, Goryshin *et al.* teach that the transposon sequences for Tn5 can be cloned into a plasmid vector and used to insert said vector into endogenous sequences. The vectors used by Goryshin *et al.* are bacterial and contain the selectable marker for antibiotic resistance (page 98, second column and vector construction described, page 99, second column). Goryshin *et al.* teaches that the transposon sequences used are mosaic indicating they are not the same (page 99, middle of second column). Further, Goryshin *et al.* teach to provide functional fragments of the Tn5 to generate a transposome for use in transposition of vectors and expression of encoded genes and given the lack of clarity for what would constitute an inside or outside end of Tn5, the teaching of Goryshin *et al.* is being interpreted to anticipated these limitations. Before administering the constructs the vectors are cut with PvuII (page 98, Table 1(A) and page 99, second column)

which is a restriction enzyme that generates blunt ends (see Gibco as evidence of restriction site). After delivering the vector to the cells, the cells are grown on a selective media containing the antibiotic kan (or G418), wherein the expression of the kanomycin resistance gene of the delivered vector is expressed sufficiently long time to allow for colonies to form (page 98, Table 1(B) and starting at bottom of page 99).

Tucker *et al.* describe an *in vivo* method using a transposition system to insert exogenous nucleic acid sequences into the chromosome of a cell (see summary in abstract). Specifically, Tucker *et al.* teach that the transposon sequences for Tn5 can be cloned into a plasmid vector and used to insert said vector into endogenous sequences of a cell. Tucker *et al.* teach that the vector is "preferably a linear polynucleotide" comprising the Tn5 sequences (column 6, lines 19-25) and that the vector contains a sequence which encodes a marker which can be detected (column 6, lines 40-52). By way of example, Tucker *et al.* reduce to practice a polynucleotide which encodes a kanamycin resistance gene which is contained between the mosaic ends of a Tn5 transposon (bridging columns 7-8). The plasmid is linearized as well as excised with PvuII and used to transfect cells. The cells are allowed to grow on kanamycin containing media and by expression of the kan^R gene, colonies are formed (see summary in Table 1, column 8).

Rolland *et al.* teach a method for the delivery and expression of a nucleic acid vector to an mammal *in vivo* (see summary in abstract and claim 1 for example). More specifically, Rolland *et al.* teach that a nucleic acid vector can be many forms of non-viral nucleic acids including RNA, cDNA and plasmid DNA (column 2, lines 37-40). Furthermore, though it is

known in the art that cDNA and RNA are linear nucleic acids, Rolland *et al.* specifically teach that whatever vector used can be provided in a linear form (column 2, lines 58-59). Rolland *et al.* teach that the vector can comprise one or more genes to be expressed (column 2, lines 58-59), and by way of example a reduction to practice using the expression and detection of the luciferase and CAT transgenes is provided (see figures 6 and 8, on sheet 5 of 8). Finally, Rolland *et al.* teach that various routes of delivery can be used including within the muscle or interstitial space of a joint (column 2, lines 30-33 and claims 5 and 8).

Thus, the teaching of Wolff *et al.*, Goryshin *et al.*, Tucker *et al.* and Rolland *et al.* for the delivery of linear nucleic acid sequences and expression of said sequences *in vivo* anticipates the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 14, 15, 18 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Rolland *et al.* (US Patent 6,514,947) in view of Budker *et al.* (Gene Therapy, 5:272-276, 1998).

Claims 1, 6, 18 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tucker *et al.* (US Patent 5,102,797) in view of Sambrook et al. (Molecular Cloning, Vol 2, section 14.5, 1989).

Applicants note the amendments to the claims to obviate the rejection over Rolland *et al.* and Tucker *et al.*, and argue for reasons set forth in traverse of the rejection made under 35 USC 102, that the claimed invention is not obvious. Initially, it is noted that Applicants do not contest that the structural limitations of the claims, *i.e.* generated by PCR or generated from a plasmid and delivered by various routes are not taught by the cited references. Additionally, it is noted that Applicants do not argue that providing any particular linear nucleic acid sequence would provide an unexpected result over that disclosed in the prior art, rather it is argued that the particular functional limitations recited in the claims for providing a linear nucleic acid sequence are not specifically taught. See Applicants' amendment, top of page 4. Applicants' arguments have been fully considered, but not found persuasive.

As explained above, because the functional limitation of practicing the method set forth in Rolland *et al.* and Tucker *et al.* anticipate the method as claimed, and lacking evidence to the

contrary, practice of the method with the delivery of any linear polynucleotide would result in the functional limitation recited in the amended claims. As set forth previously and above, Rolland *et al.* teach that a nucleic acid vector can be many forms of non-viral nucleic acids including RNA, cDNA and plasmid DNA (column 2, lines 37-40). Furthermore, though it is known in the art that cDNA and RNA are linear nucleic acids, Rolland *et al.* specifically teach that whatever vector used can be provided in a linear form (column 2, lines 58-59). Rolland *et al.* teach that the vector can comprise one or more genes to be expressed (column 2, lines 58-59), and by way of example a reduction to practice using the expression and detection of the luciferase and CAT transgenes is provided (see figures 6 and 8, on sheet 5 of 8). Finally, Rolland *et al.* teach that various routes of delivery can be used highlighting several routes known and used in the art (column 2, lines 30-33). With respect to the teachings of Tucker *et al.* the reference describes an *in vivo* method using a transposition system to insert exogenous nucleic acid sequences into the chromosome of a cell (see summary in abstract). Tucker *et al.* teach that the transposon sequences for Tn5 can be cloned into a vector and used to insert said vector into endogenous sequences of a cell. As an example, Tucker *et al.* provide a detailed example for the production of specific nucleic acid vector (figures 1-3). Importantly, Tucker *et al.* teach that the vector is "preferably a linear polynucleotide" (column 6, lines 19-25) and that the vector contains a sequence which encodes a marker which can be detected (column 6, lines 40-52). In a reduction to practice, Tucker *et al.* teach that the plasmid is linearized and the expression cassette is excised with the restriction enzyme PvuII, and the linear nucleic acid is used to transfect cells.

At the time of filing various routes of administration of polynucleotides were known and that teach that PCR amplification results in linear fragments of DNA which can be used for many molecular applications including molecular cloning. More specifically, Budker *et al.* teach a method for the efficient expression of a transgene in muscle cells of a rat using intravascular delivery (claim 14) of a non-viral nucleic acid wherein increased hydrostatic pressure is used to deliver the vector (see summaries on page 272 in second paragraph in the first column and final two paragraphs on page 276)(claim 15). Additionally, the lacZ gene expression cassette used and expressed in the delivery methods described in Budker *et al.* was obtained as a restriction fragment from the plasmid pBS-RSV-LacZ and inserted into pCI (see figure 4)(claims 7 and 19). With respect to making nucleic acid sequences by various methods, Sambrook *et al.* teach that PCR amplification results in linear fragments of DNA which can be used for many molecular applications including molecular cloning (section 14.5). The teaching of Budker *et al.* and Sambrook *et al.* are relied upon to demonstrate well known and obvious means not specifically disclosed in Rolland *et al.* and Tucker *et al.* Combining the methods disclosed by Rolland *et al.* and Tucker *et al.* with that of Budker *et al.* and Sambrook *et al.* would not provide any unexpected results, and would inherently result in any functional limitation resulting from practicing Rolland *et al.* and Tucker *et al.* alone. Given the conventional nature of methods involving PCR and delivery by injection there would be a reasonable expectation of success to obtain and deliver nucleic acid sequences as taught by Budker *et al.* and Sambrook *et al.* in the methods disclosed by Rolland *et al.* and Tucker *et al.*

Thus, it is maintained that the claimed invention of delivering a non-viral nucleic acid to cell *in vivo* made by PCR by intravascular injection as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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